Disappearance of Renal Stones in an HIV-1-Infected Patient After Reduction of Atazanavir Dose.

Disappearance of renal stones in a HIV-1-infected patient after reduction of atazanavir dose

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ABSTRACT

Several case reports have suggested the involvement of ATV in nephrolithiasis.The incidence of renal stones is approximately 10 times higher among patients on ATV/r than those on other PIs. We report a case of an HIV-1-infected patient on ATV/r with kidney stone episodes, who benefit from an atazanavir dose reduction.

Atazanavir/ritonavir administration has been recently showed to be a risk factor for symptomatic nephrolithiasis[1] .Atazanavir could promote kidney stones trough similar mechanisms to indinavir-induced urolithiasis (drug crystallization and precipitantion in the kidneys)[1].de Lastours and colleagues showed high levels of atazanavir and darunavir in urine with crystalluria in asymptomatic HIV-infected patients, being urinary atazanavir and darunavir concentrations significantly higher than plasma levels[2]. We report the first case of an HIV-1-infected patient on atazanavir/ritonavir (300/100 mg daily) with recurrent kidney stone episodes, who benefit from a atazanavir dose reduction. A 30-year old man (CDC A2), HIV-infected since 2007, without HBV or HCV co-infections, came to our attention in October 2012. The patient was taking tenofovir/emtricitabine and atazanavir/ritonavir (300/100 mg daily) since June 2011(after four years of fully suppressive first-line regimen of tenofovir/emtricitabine and efavirenz) with optimal adherence but complaining of scleral icterus. T CD4+ cell count was 903/mm^3, HIV RNA <20 copies/ml and total bilirubin 6.11 mg/dl. Family history was unremarkable for urolithiasis. Blood tests did not show any plasma lipids, kidney function (eGFR >90mL/min/1.72m^2) and uric acid levels abnormalities. He reported three kidney stones episodes in the last year (December 2011 , May and September 2012) after starting atazanavir-containing treatment. Renal echography showed thin bilateral stones (October 2012). We decided to reduce the dose of atazanavir to 200 mg daily with 100 mg of ritonavir to reduce his discomfort due to atazanavir-related jaundice, collecting paired plasma and urine samples for pharmacokinetic analysis[3]. Atazanavir C_{trough} was 1017 ng/ml in plasma and 37110 ng/ml in urine sample before dose reduction. One month after (November 2012), HIV RNA was still < 20 copies/ml and total bilurbin value was dropped to 3.30 mg/dl. On June 2013, he did not report any episodes of renal stones, but the patient continued to report discomfort for the persistent scleral icterus. Atazanavir dose was further reduced to 150 mg daily with 100 mg daily of ritonavir. On December 2013, CD4 cell count was 660/mm3, HIV RNA not detectable, and total bilurbin 1.26 mg/dl, with disappearance of scleral icterus. After thirteen months of follow up, he no longer reported any sign of urolithiasis, and a renal echography did not show any radiological findings of renal stones. At a second pharmacokinetics analysis, ATV C_{trough} was 160 and 4683 ng/ml in plasma and urine, respectively.Nephrolithiasis has been reported in patients receiving ATV/r-

containing antiretroviral therapy[2,4].Several case reports documented high concentrations of ATV in renal stones, suggesting the involvement of ATV in nephrolithiasis[4-6]. Hamada *et al* recently reported in a single center cohort study that the incidence of renal stones is approximately 10 times higher among patients on ATV/r-containing antiretroviral therapy (ART) than those on other PIs-containing ART[1].The mechanism of atazanavir/ritonavir-induced renal stone formation could be the crystallization of atazanavir, as in the case of indinavir-induced renal stones[6].Although in our case ATV concentrations were higher in urine than in plasma, as expected[2], a dramatic decrease of urine concentration (by 88%) was showed after dose reduction to boosted 150 mg daily, with disappearance of symptoms and signs of renal stones. This finding confirms the need of a threshold of ATV urinary concentration to form precipitation in crystals[2].ATV plasma concentrations are known to correlate with serum bilirubin level and switch to unboosted ATV has been described to reduce the risk of hyperbilirubinemia[8].Rockwood et al[7] found a close association between hyperbilirubinemia and the development of renal stones, supporting the association of both with plasma exposure, and, for the latter, with urinary exposure too. ATV crystalluria, in fact, has been shown to be related to duration of ATV intake, but also to be more frequent in RTV-boosted dose (300/100) as compared to unboosted 400 mg dose intakers[2]. It is noteworthy to remember that even in indinavir-intakers dose reduction and TDM were effective in case of renal stones[9]. In our case, such unconventional dose reduction allowed to continue ATV-containing effective regimen, with a clear improvement of tolerability, while maintaining virological efficacy. A dose decrease to boosted 150 mg/daily, in fact, was associated with ATV Ctrough still above the minimum effective concentration (MEC ,150 ng/ml). We could speculate that ATV Ctrough value of our patient dosed at 150 mg with 100 mg of RTV was in the expected range of unboosted ATV pharmacokinetics[8], and switch to unboosted ATV has been shown to be effective in stable patients[8]. Anyway, we recently reported the efficacy of a maintenance reduced dose of atazanavir/ritonavir in a small cohort of virologically suppressed HIV-infected patients[10].In conclusion, ATV dose reduction in stable patients reporting the occurrence of ATV-related renal stones deserves further clinical evaluation as a strategy to improve tolerability of this compound.

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